LYRICA® (pregabalin) Ⓥ eLearning System

LYRICA® (pregabalin) capsules Ⓥ Clinical Data in Fibromyalgia

Pfizer Inc

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Contents

Introduction

The information contained in this training module is for your educational purposes only. This training piece is designed to provide you with information you need on the product, the disease, and the competitive environment. It is not to be used in detailing or distributed to any third parties.

Fibromyalgia is one of the most common chronic, widespread pain conditions in the United States. The ACR estimates that fibromyalgia affects 2% to 5% of Americans, or 5.3 million people. Patients tend to present between the ages of 20 and 50. It is estimated that between 75% and 90% of people affected by fibromyalgia are women.

LYRICA® (pregabalin) Ⓥ binds with high affinity to the **alpha$_2$-delta** (α_2-δ) site, an auxiliary subunit of **voltage-gated calcium channels**, in central nervous system tissues. Although the exact mechanism of LYRICA is unknown, voltage-gated calcium channels are thought to play a key role in regulating excitatory neurotransmitter release and modulating cell membrane excitability. This suggests a mechanism through which LYRICA may decrease the neuronal hyperexcitability and resulting pain characteristic of fibromyalgia. Animal models have shown that decreasing calcium influx in hyperexcited neurons decreases the release of excitatory neurotransmitters such as **glutamate** and **substance P**.

In the United States, LYRICA is FDA-approved for:

- management of neuropathic pain associated with **diabetic peripheral neuropathy (DPN)**
- management of **postherpetic neuralgia (PHN)**
- management of fibromyalgia
- adjunctive therapy for adult patients with **partial seizures**

This module will focus on the clinical data for the use of LYRICA in fibromyalgia. Key features of LYRICA include its powerful and sustained efficacy, well-studied safety profile and tolerability profile, linear **pharmacokinetics**, high **bioavailability**, and low potential for pharmacokinetic drug interactions. Information on these other characteristics of LYRICA can be found elsewhere in the *LYRICA® eLearning System*.

Section 1 provides information about the 2 pivotal clinical trials in fibromyalgia that are listed in the LYRICA product labeling.

The module concludes with a summary, glossary of medical terms, and bibliography.

Section 1: Pivotal Clinical Trials in Fibromyalgia

Objectives

- Identify the studies in the clinical trials program for LYRICA in fibromyalgia
- Describe the primary and secondary efficacy measures used in the pivotal clinical trials for LYRICA in fibromyalgia
- Describe the patient selection criteria used in the pivotal clinical trials for LYRICA in fibromyalgia
- Describe the data analysis and presentation used in the pivotal clinical trials for LYRICA in fibromyalgia
- Describe the design of Arnold et al
- Discuss the results of Arnold et al and their significance
- Describe the design of Crofford et al
- Discuss the results of Crofford et al and their significance

The efficacy and safety of LYRICA as monotherapy for the management of fibromyalgia were established across a clinical trial program, including 2 **double-blind**, placebo-controlled, multicenter clinical trials that are listed in the LYRICA product labeling.

This section provides an overview of the key features of these trials, including the list of studies that appear in the LYRICA product labeling, the primary and secondary efficacy measures that were used, and the patient selection criteria for these key clinical trials.

In addition, this section will discuss the methods of data analysis that was used in these trials, including the differences between the last observation carried forward (LOCF), baseline observation carried forward (BOCF) analysis, and modified baseline observation carried forward (mBCOF).

Finally, this section will end with a discussion of both fibromyalgia clinical trials listed in the LYRICA product labeling.

Identify the studies in the clinical trials program for LYRICA® in fibromyalgia

Overview of the Pivotal Clinical Trials

The efficacy and safety of LYRICA for the management of fibromyalgia was established across a clinical trial program in:

- Arnold et al, a 14-week, double-blind, placebo-controlled, multicenter clinical trial (study F1 in the LYRICA product labeling)
- Crofford et al, a 6-month, randomized withdrawal clinical trial (study F2 in the LYRICA product labeling)

Table 1A lists key features of the fibromyalgia studies described in the package insert. The table and the subsequent text identify these studies by both their designation in the package insert (for example, Arnold et al) and the first author of the publication (for example, Crofford et al).

***Table 1A:* Pivotal Trials in Fibromyalgia**

Study	*Description*	*Dose Groups*
Arnold et al. *J Pain*. Sept 2008; 9(9):792-805. Study F1 in the LYRICA product labeling	• 14-week, phase III, randomized, double-blind, placebo-controlled, fixed-dose trial, including a 2-week dose-escalation phase, and a 12-week maintenance phase – the study began with a 1-week placebo run-in phase to exclude placebo responders • 745 patients	• LYRICA 300 mg/day (150 mg **BID**) • LYRICA 450 mg/day (225 mg BID) • LYRICA 600 mg/day (300 mg BID) • placebo
Crofford et al. *Pain*. June 2008;136(3): 419-431. Study F2 in the LYRICA product labeling	• randomized withdrawal study starting with an **open-label** phase to exclude LYRICA nonresponders and followed by a 6-month phase to assess the durability of the effect of LYRICA in responders: – 6-week, open-label, dose optimization phase in which 1051 patients were treated with LYRICA 300, 450, or 600 mg/day based on response and tolerability • responders (n = 566) were randomized to LYRICA or placebo for 26-week double-blind treatment; patients randomized to LYRICA received the dose that was optimized during the open-label phase and remained at the fixed dose for the 26-week treatment period	• LYRICA 300 mg/day to 600 mg/day (150 mg BID to 300 mg BID)* • placebo

** LYRICA 600 mg/day is not an approved dose for fibromyalgia, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.*

Progress Check

There may be **more than one** correct answer to each question.

1. Match each study to its description.

A	14-week phase III trial	A	Arnold et al
B	included a 6-month double-blind phase	B	Crofford et al
B	566 patients were randomized into one of the treatment groups for the double-blind phase of the study		
A	745 patients were randomized into one of the treatment groups		

Describe the primary and secondary efficacy measures used in the pivotal clinical trials for LYRICA® in fibromyalgia

Efficacy Measures

Efficacy Measures in Arnold et al (Study F1 in the LYRICA Product Labeling)

Primary Efficacy Measures

The primary efficacy measure in the **intent-to-treat (ITT) population** was the change in **mean** pain score from baseline to endpoint, which was derived from a daily pain diary recorded by patients using an 11-point scale called the Pain Intensity Numeric Rating Scale (PI-NRS). Upon awakening, patients evaluated their pain for the previous 24 hours by circling the number on the scale that best described the pain they experienced. The PI-NRS rates pain from 0 (no pain) to 10 (worst possible pain).

In addition, co-primary endpoints were conducted and included:

- Patient Global Impression of Change (PGIC), in which patients measure the change in their overall status from the beginning of the study to endpoint on a scale ranging from 1 (very much improved) to 7 (very much worse)
- Fibromyalgia Impact Questionnaire (FIQ) total score, a 20-item self-administered questionnaire that measures multiple symptoms and functions and provides an estimation of fibromyalgia impact on the patient

Table 1B lists primary efficacy measurements used in Arnold et al.

Table 1B: Arnold et al Primary Efficacy Measures

Efficacy Measure	Description
Pain Intensity Numeric Rating Scale (PI-NRS)	• PI-NRS is one of the most commonly used methods of assessing pain intensity • patients rate their pain on an 11-point scale, ranging from 0 (no pain) to 10 (worst pain possible) • a decrease in score indicates improvement • validity has been well documented; correlates well with other measures of pain intensity; is sensitive to treatments that are expected to have an impact on pain intensity • easy to administer and score
Patient Global Impression of Change (PGIC)	• patients rate on a 7-point scale (from 1 = very much improved to 7 = very much worse) the change in their overall status since the beginning of study – these are then usually grouped into 3 categories (3 levels of worsening, 1 no change, and 3 levels of improvement) – the percentage of patients in each of the 3 categories (worsening, no change, and improvement) is usually presented, rather than the overall score • the PGIC allows patients to provide an aggregate of all the components of their experience in an overall measure of their perception of the advantages and disadvantages of treatment
Fibromyalgia Impact Questionnaire (FIQ)	• patients fill out a 20-item questionnaire to assess the overall effect of fibromyalgia symptomatology – contains 10 subscales, which are combined to yield a total score – 11 of the 20 questions are related specifically to physical functioning and are scored from 0 (always able to do) to 3 (never able to do) – the remaining items assess pain, fatigue, stiffness, difficulty working, feeling rested, and symptoms of anxiousness and depression, and are scored from 0 (no impairment) to 10 (great impairment) – 2 questions are the number of days in the past week the patients felt good and the number of days they missed work • the total score ranges from 1 to 100, with higher scores indicating more impairment; in some cases, work questions are not included and the total score ranges from 0 to 80 • a decrease in score in both the subscales and the total score indicates improvement

Secondary Efficacy Measures

A number of secondary efficacy measures were used to evaluate changes in pain-related sleep interference, fatigue, mood, and other patient-reported outcomes during treatment.

These secondary measures are not described in the package insert, but are discussed in this module as background information only. The majority of these measurements, which employ questionnaires that are self-administered by the patients, are described in Table 1C.

Table 1C: Arnold et al Secondary Efficacy Measures

Efficacy Measure	Description
Pain Visual Analogue Scale (Pain VAS)	• VAS is one of the most commonly used methods of assessing pain intensity • patients rate their pain on a 100 mm horizontal line ranging from 0 (no pain) to 100 (worst possible pain) • a decrease in score indicates improvement • validity has been well documented; correlates well with other measures of pain intensity; is sensitive to treatments that are expected to have an impact on pain intensity • the higher number of possible responses compared to the PI-NRS (101 versus 11) makes the VAS potentially more sensitive than the PI-NRS
Sleep Quality Score from the Daily Sleep Diary	• patients rate the quality of sleep during the past 24 hours on an 11-point numeric rating scale, ranging from 0 (best possible sleep) to 10 (worst possible sleep) • a decrease in score indicates improvement
Medical Outcomes Study-Sleep (MOS-Sleep) Scale	• patients rate their sleep using 12-item assessment that consists of 7 subscales and a 9-item over all Sleep Problems Index • higher scores indicate more impairment except for sleep adequacy, quantity of sleep, and optimal sleep
Multidimensional Assessment of Fatigue (MAF)	• consists of a 16-item questionnaire that measures 4 dimensions of fatigue • patients rate the items from 1 (not at all) to 10 (a great deal) • scores are combined to yield a Global Fatigue Index, ranging from 1 to 50 • a decrease in score indicates improvement
Short-Form-36 Health Questionnaire (SF-36)	• a 36-item, quality-of-life scale that assesses 8 health domains • scores range from 0 (very poor health) to 100 (best health) • an increase in score indicates improvement
Hospital Anxiety and Depression Scale (HADS)	• patient-rated scale consisting of 14 items that includes two 7-item subscales for anxiety and depression • scores range from 0 to 21 for each subscale • a decrease in score indicates improvement

Efficacy Measures in Crofford et al (Study F2 in the LYRICA Product Labeling)

Primary Efficacy Measure

The pre-specified primary efficacy measure in the ITT population was the loss of therapeutic response (LTR), which was defined as:

- reduction of <30% in pain scores from the open-label baseline of the study in 2 consecutive visits during the double-blinded portion of the study
- worsening of fibromyalgia symptoms that required the use of alternate treatment

It is important to note that in terms of LTR data, the FDA required a more stringent definition (after the study was complete) that differed from the one used by Crofford et al in their 2008 publication. The FDA definition for loss of therapeutic response included patients who discontinued treatment due to adverse events. Those that discontinued due to an adverse event were considered to have lost therapeutic response.

Secondary Efficacy Measures

The secondary efficacy measures included PGIC, FIQ, MOS-Sleep Scale, MAF, HADs, and SF-36, and were used to evaluate changes in pain-related sleep interference, fatigue, mood, and other patient-reported outcomes during treatment.

These secondary measures are not described in the package insert, but are discussed in this module as background information only. The majority of these measurements employed questionnaires that are self-administered by the patients.

Click on the icon to reinforce what you have learned about the primary efficacy measures for Arnold et al and Crofford et al.

Progress Check

There may be **more than one** correct answer to each question.

1. Match each study to its primary efficacy measure.

A	change in mean pain score based on the PI-NRS	A	Arnold et al
B	loss of therapeutic response	B	Crofford et al
A	PGIC (co-primary efficacy measure)		
A	FIQ (co-primary efficacy measure)		

Describe the patient selection criteria used in the pivotal clinical trials for LYRICA® in fibromyalgia

Inclusion and Exclusion Criteria

Although Arnold et al and Crofford et al have different study designs and different endpoints, they did have some things in common, including key aspects of the inclusion and exclusion criteria and the medications that were prohibited. Table 1D provides information on the inclusion criteria common to both trials for enrolling patients in these trials.

Table 1D: **Management of Fibromyalgia Trials in the Package Insert: Inclusion Criteria**

- Male or female of any race ≥18 years old
- Females must not have been pregnant or lactating, and additionally be postmenopausal, surgically sterilized, or using an appropriate method of contraception
- Diagnosis of fibromyalgia using the ACR criteria:
  - history of widespread pain for 3 months
  - pain present at 11 or more of the 18 specific tender point sites
- Have recorded a score of ≥40 mm on the Pain VAS at screening and enrollment/randomization
- Willing to comply with study procedures
- Informed consent

Table 1E provides information on the exclusion criteria for enrolling patients in these trials.

Table 1E: **Management of Fibromyalgia Trials in the Package Insert: Exclusion Criteria**

- Evidence of inflammatory muscle or rheumatologic disease
  - abnormal antinuclear antibody ≥3 U or rheumatoid factor >80 IU/mL
- Previous participation in a LYRICA clinical trial
- Severe psychiatric illness (including major depressive disorder)
- Severe medical illness
- **Creatinine clearance (CL_{cr})** ≤60 mL/min
- Pending Worker's Compensation, Workman's Compensation, civil litigation, disability claims, or out-of-court settlements for claims pertinent to the subject's fibromyalgia, or currently receiving monetary compensation as a result of any of these

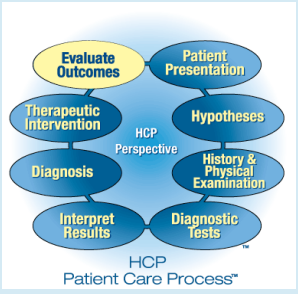
Prohibited medications included:

- medications used for relief of pain associated with fibromyalgia, such as muscle relaxants, tricyclic antidepressants, selective **serotonin** reuptake inhibitors, venlafaxine, antiepileptic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and other prescription **analgesics**
- medications used for relief of insomnia, such as benzodiazepines and hypnotics
- drugs that can cause irreversible retinotoxicity, such as thioridazine, vigabatrin, hydroxychloroquine, and deferoxamine

Click on the icon to read about the results of treatment for Amy, a patient with fibromyalgia.

CASE STUDY

Amy — A Patient with Fibromyalgia



Dr. Harris, a rheumatologist, has prescribed LYRICA 150 mg/day (75 mg BID) to manage 41-year-old Amy's fibromyalgia. He tells Amy to come back for a follow-up appointment after taking LYRICA for 4 weeks so he can evaluate treatment effectiveness and any adverse events that Amy might experience related to treatment.

When Amy returns for her follow-up appointment 4 weeks later, she tells Dr. Harris that she believes her treatment with LYRICA has helped. She says that her fatigue, chronic widespread pain, stiffness, and clumsiness have all improved. Amy tells Dr. Harris that in the last 3 weeks, she hasn't had any days where her fibromyalgia pain was so bad that she couldn't get out of bed. She also tells Dr. Harris that she has found the fibromyalgia support group that she joined to be very helpful, and she has started an exercise program under the supervision of her primary care physician. So, all-in-all, she feels like she is doing *much* better.

Dr. Harris asks Amy if she has noticed any side effects from taking LYRICA. Amy replies that the only thing she has noticed is that she has felt dizzy on 1 or 2 occasions while gardening, but the spells were very short and did not last more than 5 minutes or so.

Based on what Amy has told Dr. Harris regarding the improvement in her fibromyalgia symptoms, Dr. Harris decides not to make any adjustments to her dose of LYRICA. Dr. Harris decides to keep Amy on LYRICA 75 mg BID (150 mg/day) and continue to monitor her progress and treatment-related adverse effects.

Progress Check

There may be **more than one** correct answer to each question.

1. Patients were eligible for inclusion in these trials if they:
   - ***A*** ***had a diagnosis of fibromyalgia based on the ACR criteria.***
   - ***B*** ***were at least 18 years old.***
   - C were considered to have fibromyalgia based on the clinical judgment of the investigator, even if they had less than 11 of 18 tender points.
   - D had evidence of inflammatory muscle or rheumatic disease.

Describe the data analysis and presentation used in the pivotal clinical trials for LYRICA® in fibromyalgia

Data Analysis and Presentation

As you learn about and then discuss the data from the clinical trials of LYRICA in fibromyalgia, it is important that you understand how these data were obtained. One consideration is how data are handled from patients who drop out before the end of the trial. Two key points are:

- Are data from patients who dropped out included at all? This question refers to the use of ITT versus observed cases analysis.
- If data from patients who dropped out are included, how are they handled? This question refers to the use of last observation carried forward (LOCF) versus baseline observation carried forward (BOCF) analysis or modified baseline observation carried forward (mBOCF).

Intent-to-Treat versus Observed Cases

The analysis for these studies was conducted on an ITT basis. In Arnold et al, the ITT population was defined as all randomized patients who took at least one dose of study medication. In Crofford et al, ITT was defined as all subjects who were randomized at the end of the open-label treatment phase. Observed cases usually refer to the patients who actually completed a trial. Analyzing data on an ITT basis is a more rigorous method of analysis.

LOCF versus BOCF and mBOCF

The second question is what to report for the data points for a subject after that subject has dropped out of the trial. The traditional method of reporting these data has been last observation carried forward (LOCF). ***In general terms, LOCF means that the last data measurement for a patient who dropped out is also used for the value at all subsequent measurement times, including study endpoint.***

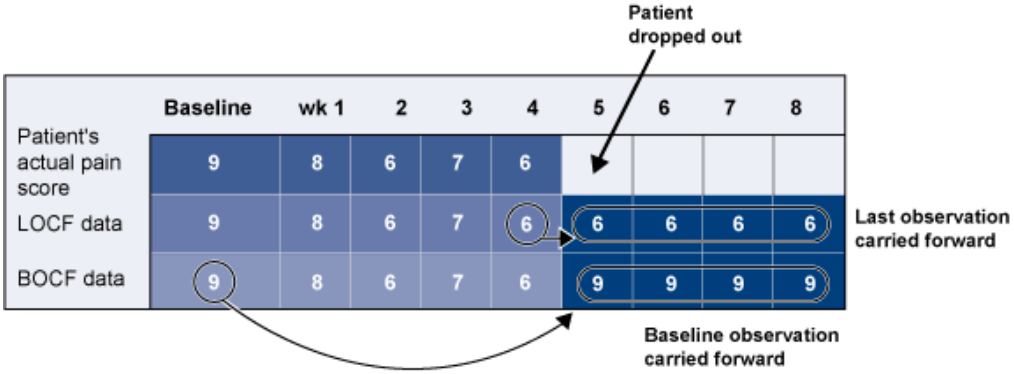
The FDA division that evaluates analgesics now requires the use of baseline observation carried forward (BOCF) analysis for chronic pain conditions. ***With BOCF analysis, if patients drop out of the trial, instead of using their last measurement while on treatment and carrying it forward (LOCF), their original baseline measurement is carried forward — eliminating any measurements they reported during the time they did receive treatment.***

Because the *baseline* values (before any treatment) are reported for patients who drop out, BOCF data usually result in lower response rates and yield smaller treatment effects compared to LOCF data, especially when more patients drop out in the groups receiving active treatment than in the one receiving placebo.

It is important to note that some fibromyalgia data in the LYRICA package insert and marketing materials (eg, the visual aid) may present a modified BOCF (mBOCF) analysis, rather than straight BOCF data (which is also in the package insert) or LOCF data (which is used in the published clinical study). ***The mBOCF analysis censors patients who discontinue due to adverse events so that their baseline score is carried forward, but carries the last observation forward for patients who discontinue for other reasons (eg, lost to follow-up).***

Figure 1A illustrates the difference between LOCF and BOCF analysis for the data from an individual patient.

Figure 1A: LOCF versus BOCF and mBOCF Analysis for an Individual Patient



In this example, the patient dropped out after week 4
- in LOCF analysis, the week 4 pain score would be used for the rest of the evaluations
- in BOCF analysis, the baseline pain score would be used for the rest of the evaluations
- in mBOCF analysis, the baseline pain score (9) would be used for the rest of the evaluations if the patient dropped out of the study due to an adverse event, and the week 4 pain score (6) would be used if the patient dropped out of the study for other reasons (eg, lost to follow-up).

BOCF and mBOCF data are reported in the LYRICA package insert for fibromyalgia. All published studies are reported using LOCF data. For fibromyalgia, only BOCF and mBOCF data from the package insert can be discussed with physicians.

Click on the icon to reinforce what you have learned about LOCF versus BOCF analysis in clinical studies.

Progress Check

There may be **more than one** correct answer to each question.

1. Which of the following is (are) **true** regarding how the data were analyzed in these trials?

   A ***The analysis was done on an ITT basis for the primary endpoints.***

   B ***The FDA now requires the use of BOCF analysis for chronic pain conditions.***

   C BOCF analysis means that if a patient drops out, the score on the last visit is used as the score for the remainder of the trial.

   D BOCF analysis means that if a patient drops out, the data from that patient are not used at all in the analysis.

Describe the design of Arnold et al

Arnold et al Design

Arnold et al (study F1 in the LYRICA product labeling), which was published in the *Journal of Pain* in September 2008 by Arnold et al, began with a 1-week, **single-blind**, placebo run-in phase. Patients were included or excluded using the criteria listed earlier in this section, as well as the following inclusion criteria:

- at least 4 pain diaries in the last 7 days should have been completed by the patient at randomization
- the average pain score derived from these diaries was ≥4

Patients who showed a placebo response (≥30% decrease on the Pain VAS from baseline) were discontinued from the study at the end of the run-in phase. These patients were discontinued because the study authors were interested in observing a treatment effect of LYRICA. In other words, they wanted to optimize entry into the study of LYRICA responders. This kind of study design is known as an "enrichment study design." It is important note that those who entered the next phase of the study were still randomized to placebo. This was followed by a 2-week dose escalation phase, and then a 12-week, double-blind treatment phase, for a total of 14 weeks of double-blind treatment. Patients who completed or withdrew from the double-blind phase could elect to continue in open-label follow-on studies or discontinue treatment.

In Arnold et al, doses of LYRICA were escalated over a double-blind period of 2 weeks. Patients then remained at a fixed dose for the remainder of the double-blind phase (12 weeks). The baseline mean pain score in this trial was 6.7.

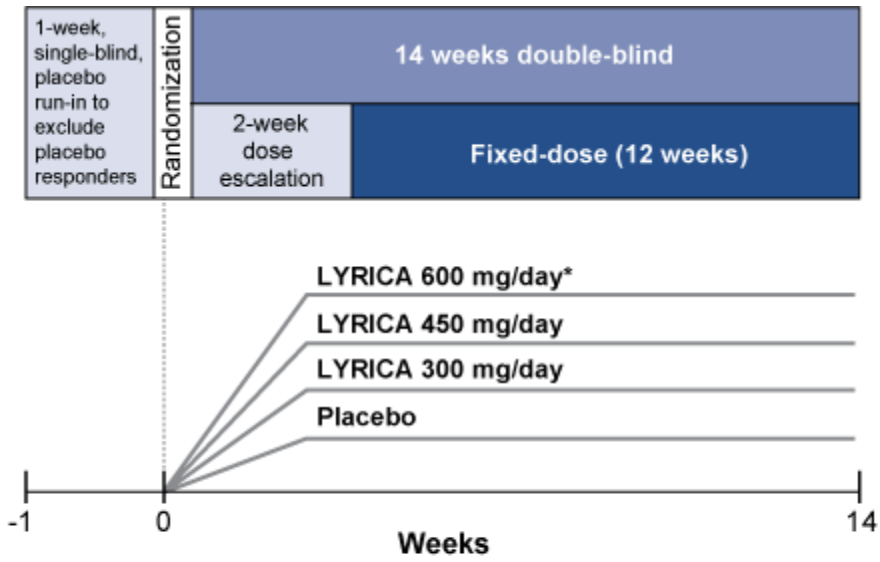
A total of 745 patients were randomized to 1 of the following groups:

- placebo (n = 184)
- LYRICA 300 mg/day (150 mg BID) (n = 183)
- LYRICA 450 mg/day (225 mg BID) (n = 190)
- LYRICA 600 mg/day (300 mg BID) (n = 188)

Please note that LYRICA 600 mg/day is not an approved dose for fibromyalgia, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.

After the conclusion of the double-blind fixed-dose study, 418 patients went on to enter the open-label follow-on study. Figure 1B depicts the design of Arnold et al.

Figure 1B: Arnold et al Study Design



* LYRICA 600 mg/day is not an approved dose for fibromyalgia.

Arnold et al included a 1-week baseline phase and a 14 week double-blind phase.

Adapted from Arnold et al

Endpoints

The objective for Arnold et al was to evaluate the efficacy and safety of LYRICA compared with placebo treatment for the symptomatic relief of fibromyalgia.

The primary endpoint was the endpoint mean pain score, which was derived from a daily pain diary recorded by patients using the PI-NRS in the intent-to-treat (ITT) population. The co-primary endpoints were the PGIC and FIQ. Table 1F summarizes the primary endpoints and also lists the secondary endpoints.

***Table 1F:* Arnold et al Endpoints**

Primary and Co-primary Efficacy Endpoints	*Secondary Efficacy Endpoints*
• Primary endpoint: mean pain score, derived from daily pain diary PI-NRS • Co-primary endpoints: – PGIC (at termination visit) – FIQ total score (at termination visit)	• Sleep quality • MOS Sleep Scale • MAF • SF-36 • HADS

These secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to reinforce what you have learned about the endpoints in Arnold et al.

Progress Check

There may be **more than one** correct answer to each question.

1. What was the primary endpoint for Arnold et al?
   - ***A*** ***mean pain score***
   - B PGIC
   - C FIQ
   - D time to loss of therapeutic response

2. The double-blind phase of Arnold et al included 3 weeks of dose escalation and 14 weeks of fixed-dose treatment.
   - A true
   - ***B*** ***false***

Discuss the results of Arnold et al and their significance

Arnold et al Results and Significance

When reviewing data from Arnold et al, it is important to remember the following 4 points:

- BOCF and mBOCF data are in the package insert for fibromyalgia, and published studies use LOCF data.
- For fibromyalgia, only BOCF and mBOCF data from the package insert can be discussed with physicians.
- LYRICA 600 mg/day is not an approved dose for fibromyalgia, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.
- The secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Primary Efficacy Measure: Mean Pain Score at Endpoint

Patients in the LYRICA 450 mg/day and LYRICA 600 mg/day treatment groups showed significant improvement in endpoint mean pain score compared with patients receiving placebo (based on mBOCF analysis).

Table 1G shows the mean change in pain scores for the different treatment groups.

Table 1G: **Mean Change in Pain Score (Modified BOCF) at Endpoint**

Treatment	*Mean Change in Pain Score* *mBOCF†*
Placebo	-1.02
LYRICA 300 mg/day	-1.55 (*P*=.0125)*
LYRICA 450 mg/day	-1.63 (*P*=.0102)*
LYRICA 600 mg/day**	-1.56 (*P*=.0125)*

* *Statistically significant versus placebo*

† *The endpoint mean pain score is based on the modified BOCF analysis.*

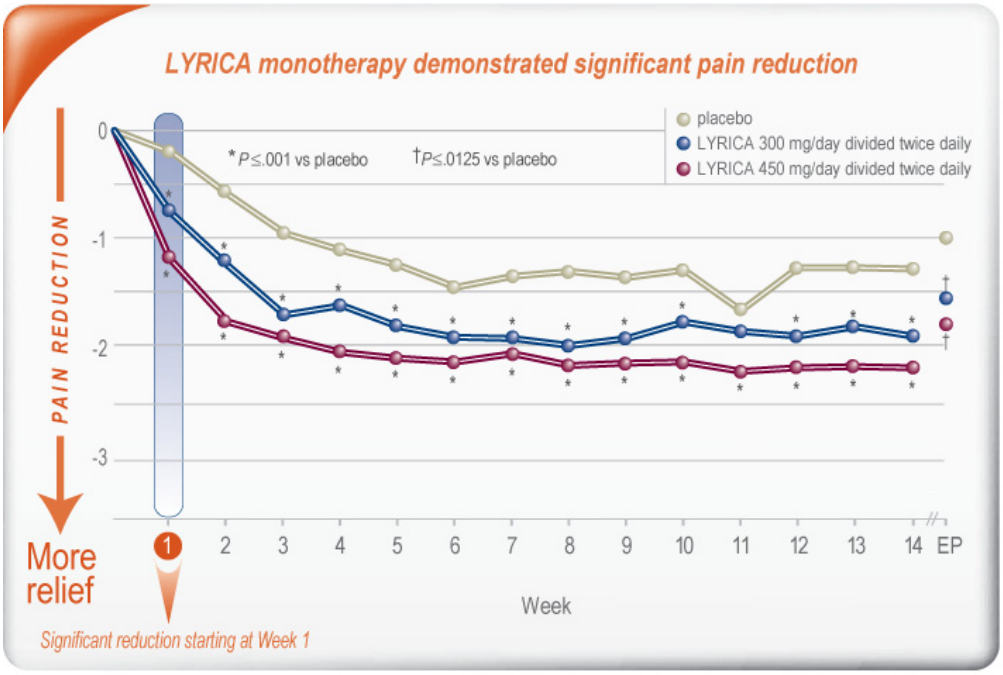
** *LYRICA 600 mg/day efficacy data are not to be detailed.*

Weekly Mean Pain Scores

All 3 LYRICA treatment groups were significantly improved over placebo at all weeks from week 1 to week 14, except the LYRICA 300 mg/day group at week 11, when statistical significance was not reached.

Figure 1C shows the decrease in mean pain scores on a week-by-week basis for LYRICA 300 mg/day and 450 mg/day, the only 2 dosing regimens that have been FDA-approved for the management of fibromyalgia.

Figure 1C: Weekly and Endpoint Mean Change in Pain Scores (mBOCF) for LYRICA 300 mg/day and 450 mg/day



Arnold et al shows the decrease in mean pain scores on a week-by-week basis for LYRICA 300 mg/day and 450 mg/day, the only two dosing regimens FDA-approved for the management of fibromyalgia. Note that both treatment groups showed statistically significant improvement over placebo at all weeks from week 1 to week 14, except the LYRICA 300 mg/day group at week 11, when statistical significance was not reached.

Adapted from Arnold et al

Proportion of Responders

Subjects with ≥30% decrease in mean pain score from baseline to endpoint were considered to be responders. Subjects with ≥50% decrease in mean pain score from baseline to endpoint were also evaluated. Subjects with ≥30% decrease in mean pain score from baseline to endpoint were considered to be responders. Subjects with ≥50% decrease in mean pain score from baseline to endpoint were also evaluated. Table 1H shows these data for mBOCF analysis.

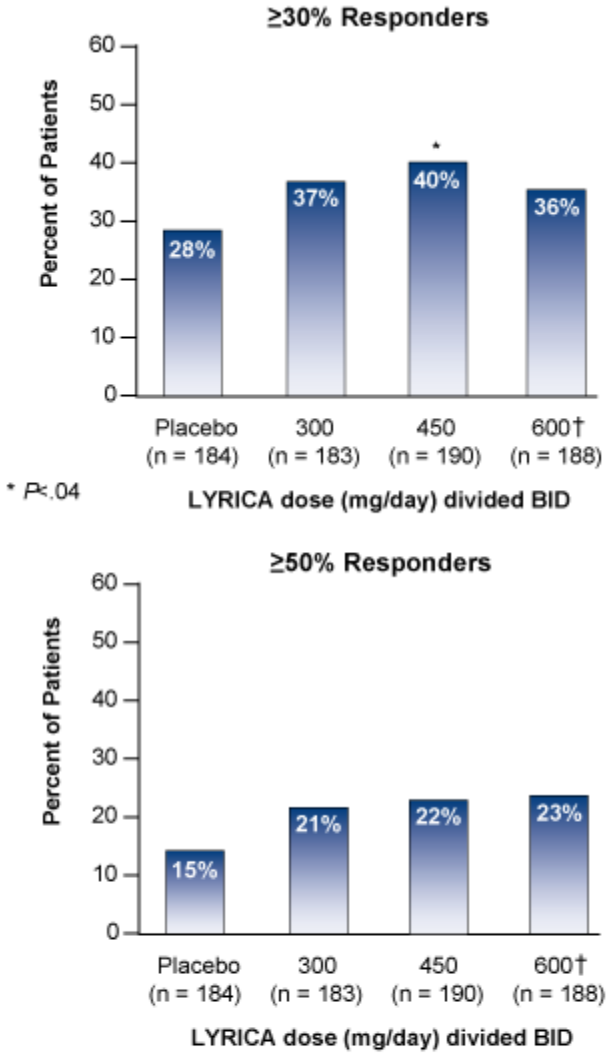
Table 1H: Proportion of Responders (mBOCF)

Treatment	≥30% Decrease in Mean Pain Score (mBOCF)	≥50% Decrease in Mean Pain Score (mBOCF)
Placebo	28%	15%
LYRICA 300 mg/day	**37%**	**21%**
LYRICA 450 mg/day	40%*	22%
LYRICA 600 mg/day**	**36%**	**23%**

**P <.05*
*** LYRICA 600 mg/day efficacy data are not to be detailed.*

Figure 1D shows both groups of responders for mBOCF data.

Figure 1D: Proportion of Pain Responders in Arnold et al (mBOCF)



† LYRICA 600 mg/day is not an approved dose for fibromyalgia.

In Arnold et al, subjects with ≥30% decrease in mean pain score from baseline to endpoint were considered to be responders, and for this group, the LYRICA 450 mg/day group was statistically significantly higher than placebo with the mBOCF analysis. Subjects with ≥50% decrease in mean pain score from baseline to endpoint were also evaluated, but none of the LYRICA groups were statistically significantly higher than placebo with the mBOCF analysis.

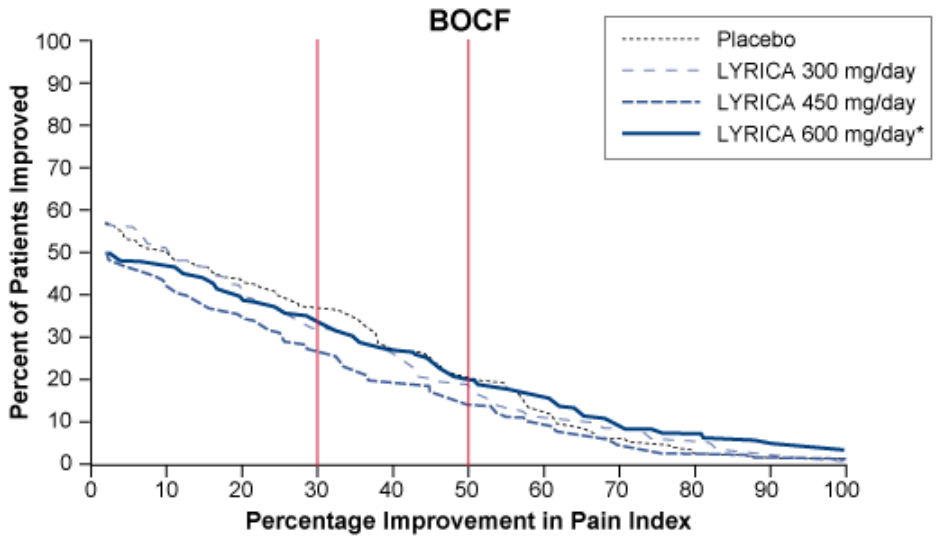
Adapted from Data on File, Pfizer Inc

Continuous Response Profile

The overall response profile was created to provide a visual display of the relative benefit of various doses across the entire range of response. In general, the overall response profiles for the 3 LYRICA groups were similar to each other, and all 3 LYRICA treatment groups clearly separated from the placebo treatment group. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 1E shows the continuous response profile, the fraction of patients achieving given degrees of improvement at any given time point. The BOCF line graph in Figure 1E can be found in the LYRICA package insert. The BOCF results are cumulative, and patients who did not complete the study were assigned 0% improvement.

Figure 1E: Continuous Response Profile (BOCF) in Arnold et al



* LYRICA 600 mg/day is not an approved dose for fibromyalgia.

In Arnold et al, the continuous response for the 3 LYRICA treatment groups appeared to be similar and clearly separated from the placebo group. The continuous response profile is the percent reduction in pain from baseline to endpoint (x-axis) and the corresponding percent of patients achieving that level of pain reduction or greater (y-axis).

Adapted from Data on File, Pfizer Inc, and the LYRICA package insert, 2009

Co-Primary Efficacy Measures: PGIC and FIQ

Because there were positive results for the primary endpoint mean pain score, the additional co-primary outcome measures (PGIC and FIQ) were evaluated.

Table 1I shows the overall percentages of subjects reporting at least minimal improvement in global impressions of change at endpoint on the PGIC.

Table 1I: **PGIC Overall Percentage of Subjects Reporting at Least Minimal Improvement**

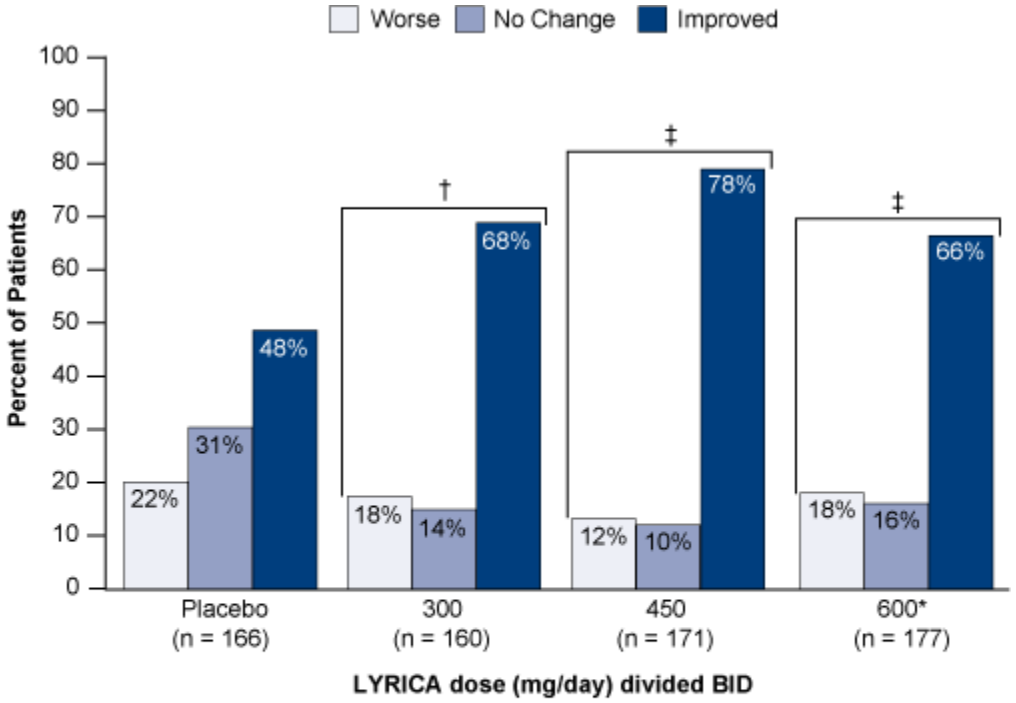
Patient Group	*Percentage*
Placebo	48% (CI 40, 55)
LYRICA 300 mg/day	68% (*P*<.01) (CI 61, 75)
LYRICA 450 mg/day	78% (*P*<.01) (CI 72, 84)
LYRICA 600 mg/day*	66% (*P*<.01) (CI 59, 73)

** LYRICA 600 mg/day efficacy data are not to be detailed.*

Significant improvements were seen in all 3 LYRICA treatment groups. Although LYRICA was studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.

Figure 1F shows the percentage of patients reporting any improvement, no change, or any worsening for each treatment group.

Figure 1F: PGIC Overall Percentage of Subjects Reporting at Least Minimal Improvement in Arnold et al



† $P<.01$ for the overall comparison of the group versus placebo
‡ $P<.001$ for the overall comparison of the group versus placebo
* LYRICA 600 mg/day is not an approved dose for fibromyalgia.

In Arnold et al, there was a significant difference between each LYRICA group overall versus placebo on the PGIC.

Adapted from Data on File, Pfizer Inc

Patients in the LYRICA 450 mg/day and LYRICA 600 mg/day* groups showed significant improvements over placebo on the FIQ total score.

[*] *LYRICA 600 mg/day efficacy data are not to be detailed.*

Secondary Efficacy Measures

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to view important information about what can and cannot be said about the Arnold et al reprint with a healthcare provider.

Click on the icon to reinforce what you have learned about the results of Arnold et al.

Progress Check

1. In Arnold et al, the proportion of responders (mBOCF) who experienced a ≥30% decrease in mean pain score was _____ in the LYRICA 450 mg/day treatment group.
   - A 20%
   - ***B 40%***
   - C 60%
   - D 80%

2. In Arnold et al, the proportion of ≥30% responders _____ compared with placebo in the BOCF analysis.
   - A was significantly greater for all doses of LYRICA
   - ***B was significantly greater for only the LYRICA 450 mg/day dose***
   - C was numerically but not significantly greater for any LYRICA group

Describe the design of Crofford et al

Crofford et al Design

Crofford et al (study F2 in the LYRICA prescribing information), which was published in *Pain* in June 2008 by Crofford et al, began with a 1-week baseline phase, followed by a 6-week, open-label, dose-optimization phase in which 1051 patients were treated with LYRICA 300, 450, or 600* mg/day. Patients were included or excluded using the criteria listed earlier in this section. In order to proceed to the double-blind phase, patients had to have:

- at least 50% reduction in Pain VAS from open-label enrollment to the end of the open-label period
- rated overall improvement on PGIC as "much improved" or "very much improved" at the end of the open-label period

Of the 1051 patients, 566 patients completed the open-label phase and responded to LYRICA. These 566 patients then continued to the 26-week double-blind treatment phase. These responders were randomized to:

- placebo (n = 287)
- LYRICA 300 mg/day, 450 mg/day, or 600 mg/day (n = 279)

Subjects who were randomized to placebo were tapered off LYRICA over 1 week; subjects who had received LYRICA in the open-label phase and who were randomized to LYRICA remained at the same dose.

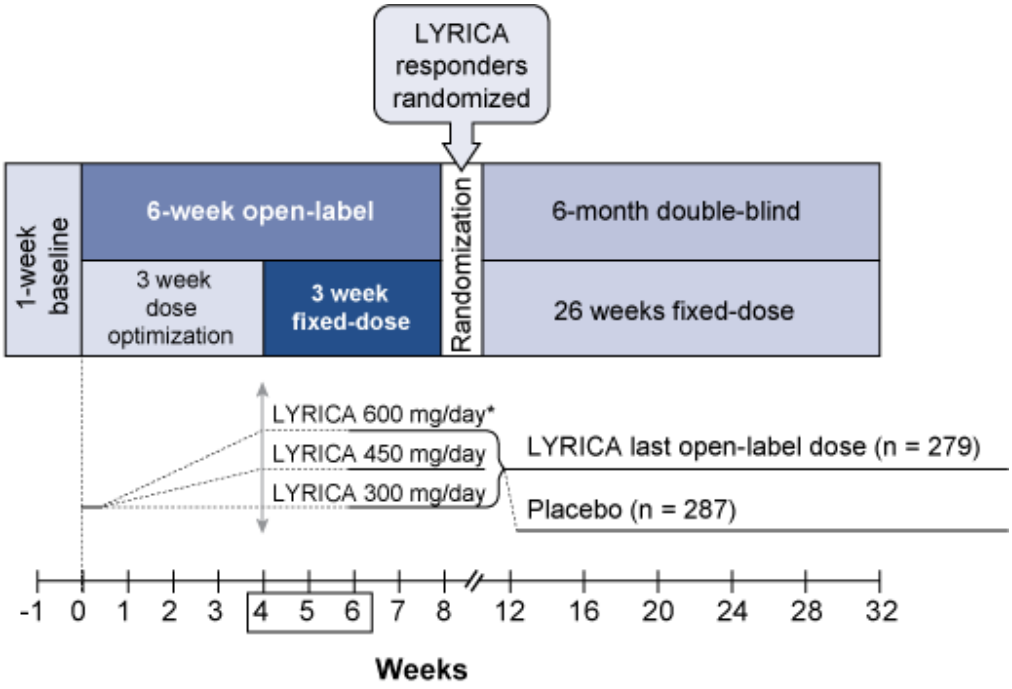
The following are the patient numbers for each dose:

- LYRICA 300 mg/day (150 mg BID) (n = 63)
- LYRICA 450 mg/day (225 mg BID) (n = 73)
- LYRICA 600 mg/day (300 mg BID)* (n = 143)

* *LYRICA 600 mg/day is not an approved dose for fibromyalgia, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.*

Figure 1G illustrates the phases of the study design for Crofford et al.

Figure 1G: Crofford et al Study Design



Responder: ≥50% reduction in pain (VAS) & PGIC much or very much improved at weeks 4 or 5, and 6.
Clinic visits: Weeks 1, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32 (follow-up week 33).

* LYRICA 600 mg/day is not an approved dose for fibromyalgia.

The study design of the durability of effect in Crofford et al included a 1-week baseline phase, 6-week open-label dose optimization phase, and 26-week fixed-dose, double-blind phase.

Adapted from Crofford et al

The activities that occurred in each phase of Crofford et al are described in Table 1J.

Table 1J: Crofford et al Design

Phase	Description
Baseline	• 1 week • subjects evaluated for inclusion/exclusion criteria
Open-label dose optimization	• 6 weeks • starting dose of 150 mg/day LYRICA • escalated to 300 mg/day LYRICA by the end of the first week • dose could be further increased at weekly intervals based on pain response and tolerability to: – LYRICA 450 mg/day (those who did not tolerate this dose were returned to LYRICA 300 mg/day) – LYRICA 600 mg/day* (those who did not tolerate this dose were returned to LYRICA 450 mg/day)
Double-blind treatment	• 26 weeks • responders during the open-label period entered the double-blind treatment and were randomized to LYRICA or placebo – responders were defined as those meeting the following 2 criteria at 2 consecutive visits: at least a 50% reduction in pain from baseline and "much improved" or "very much improved" on the PGIC – those randomized to LYRICA remained on the same dose they were receiving at the end of the dose optimization phase – those randomized to placebo were tapered off LYRICA during the first week
Follow-up	• all subjects were to complete a follow-up visit 1 week after terminating the study either for study completion or early withdrawal – this included non-responders at the end of the open-label phase

* *LYRICA 600 mg/day efficacy data are not to be detailed.*

Click on the icon to reinforce what you have learned about the study design for Crofford et al.

Endpoints

While Arnold et al evaluated improvement on its efficacy measures, the primary efficacy measure in Crofford et al was the ***time to loss of therapeutic response*** (***time to worsening***). This was defined as either of the following:

- the time it took for a patient's responses on the Pain Visual Analogue Scale (Pain VAS) to worsen to within 30% of their open-label baseline score during 2 consecutive visits during the double-blind phase, *or*
- worsening of fibromyalgia symptoms necessitating an alternative treatment per the clinical judgment of the primary investigator

As noted previously, the Pain VAS is a 100 mm horizontal line on which the subject rates his or her pain from 0 ("no pain") to 100 ("worst possible pain"). At each study visit, subjects were asked to use the Pain VAS to rate their pain for the past week. For example, if the patient's baseline score was 90, and subsequent scores were 70, 60, and 50, but then increased back to 70, and then 75, the patient would be classified as demonstrating a loss of therapeutic response because their pain score had come to within 30% of their original pain score.

The primary endpoint was assessed in the ITT population. The efficacy endpoints of this study are shown in Table 1K.

***Table 1K:* Crofford et al Endpoints**

Primary Efficacy Endpoint	*Secondary Efficacy Endpoints*
• Time to loss of therapeutic response as determined by: – the Pain VAS worsening to within 30% of the open-label baseline score during 2 consecutive visits of the double-blind phase ***or*** • worsening of fibromyalgia symptoms requiring alternative treatment as per investigator	• Time to worsening of: – FIQ – PGIC • Time to worsening of: – MOS-Sleep Scale – MAF – SF-36 • For each of these secondary endpoints, worsening was defined as worsening to within 30% of the open-label baseline score

It is important to note that the FIQ and PGIC secondary endpoints are included in the LYRICA product labeling; therefore, the results can be detailed. The MOS-Sleep Scale, MAF, and SF-36 secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on the MOS-Sleep Scale, MAF, or SF-36 secondary endpoints, you should refer him or her to Pfizer Medical Information.

Progress Check

1. What was the primary endpoint for Crofford et al?
   - A endpoint mean pain score
   - B co-primary endpoints: PGIC and FIQ
   - ***C time to loss of therapeutic response***

2. Patients in the double-blind phase of Crofford et al who were randomized to LYRICA:
   - A started at the lowest dose of LYRICA (300 mg/day) and then could be escalated to 600 mg/day based on tolerability and response.
   - B received placebo for the first week and then were randomized to LYRICA 150, 300, or 450 mg/day.
   - ***C were randomized to placebo or remained on the same dose of LYRICA they were receiving at the end of the dose optimization phase.***

Discuss the results of Crofford et al and their significance

Crofford et al Results and Significance

Crofford et al was designed to assess the beneficial effect of LYRICA in treating fibromyalgia in patients who initially experienced improvement in both PGIC and pain related to fibromyalgia. Although the study succeeded in proving the durability of LYRICA in relieving pain associated with fibromyalgia, it also showed that not all patients treated with LYRICA can maintain a response to treatment.

It is important to remember the following 4 points:

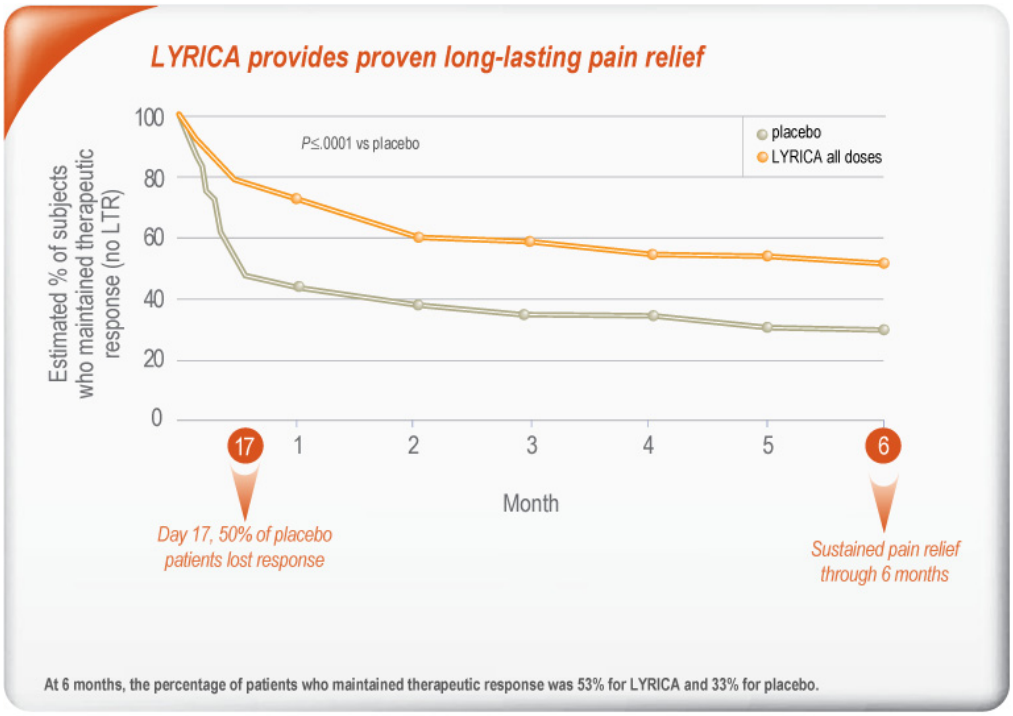
- BOCF and mBOCF data are in the package insert for fibromyalgia, and published studies use LOCF data.
- For fibromyalgia, only BOCF and mBOCF data from the package insert can be discussed with physicians.
- LYRICA 600 mg/day is not an approved dose for fibromyalgia, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.
- The secondary endpoints (except for FIQ and PGIC) are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Primary Efficacy Measure: Time to Loss of Therapeutic Response

It is important to note that in terms of loss of therapeutic response (LTR), the FDA used a more stringent definition that differed from the one used by Crofford et al in their 2008 publication. The FDA definition for loss of therapeutic response included patients who discontinued treatment due to adverse events. Those that discontinued due to an adverse event were considered to have lost therapeutic response. Applying this FDA definition, it took 17 days for half the placebo group to lose therapeutic response.

When using the mBOCF analysis (definition of LTR mandated by FDA) at day 17, 50% of the placebo patients lost therapeutic response. At day 158, 50% of pregabalin patients lost therapeutic response. Figure 1H shows the time to loss of therapeutic response in days (using the FDA definition) for the LYRICA patients versus the placebo patients.

Figure 1H: Median Time to Loss of Therapeutic Response (mBOCF) in Crofford et al*



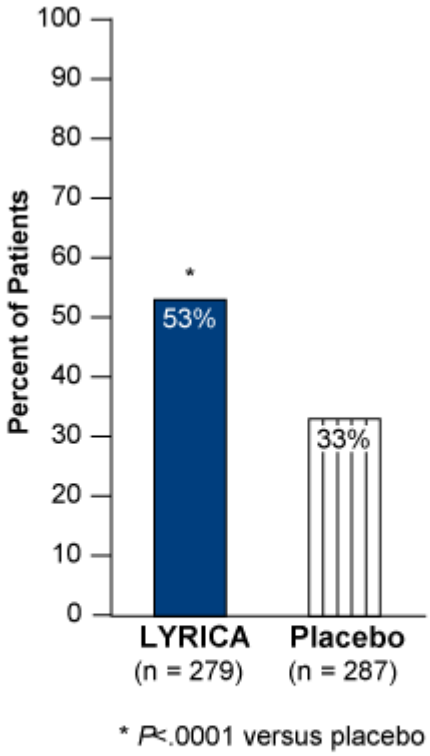
In Crofford et al, the time to loss of therapeutic response (LTR) for all patients taking LYRICA was significantly longer than that for patients taking placebo. By Day 17, 50% of the patients in the placebo group had LTR. The time at which half the LYRICA patients had lost therapeutic response was longer than the study duration.

Adapted from Crofford et al

When the individual LYRICA dose groups were compared with placebo, each LYRICA treatment group was associated with a significantly longer time to loss of therapeutic response than placebo.

The data for patients who remained on the study drug and maintained a therapeutic response to week 26 are illustrated in Figure 1l.

Figure 1l: Percentage of Patients Who Maintained a Therapeutic Response (mBOCF) for up to 6 Months in Crofford et al



By the end of the 6-month double-blind phase of Crofford et al, 53% of patients receiving LYRICA remained on the study drug and maintained therapeutic response compared with 33% for placebo (*P*<.0001).

Adapted from LYRICA package insert, 2009

Click on the icon to reinforce what you have learned about the primary efficacy measure of Crofford et al.

Secondary Efficacy Measures: FIQ and PGIC

Recall that the FIQ and PGIC secondary endpoints are included in the LYRICA product labeling; therefore, these results can be detailed:

- Treatment with LYRICA resulted in a longer time to loss of response based on the FIQ. Time to worsening of the FIQ was defined as the time to a 1-point increase from double-blind baseline in each of the subscales, and a 5-point increase from double-blind baseline evaluation for the FIQ total score.
- Treatment with LYRICA also resulted in a longer time to loss of overall assessment of patient status, as measured by the PGIC. Time to PGIC lack of improvement was defined as time to PGIC assessments indicating less improvement than "much improvement."

The MOS-Sleep Scale, MAF, and SF-36 secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to view important information about what can and cannot be said about the Crofford et al reprint with a healthcare provider.

Progress Check

There may be **more than one** correct answer to each question.

1. In Crofford et al:
   - ***A*** ***the time to loss of therapeutic response was significantly longer for patients treated with LYRICA compared to those treated with placebo.***
   - ***B*** ***the median time to loss of therapeutic response was longer than the study duration for the patients who received LYRICA.***
   - C while the time to loss of therapeutic response was significantly longer for patients treated with LYRICA as a whole, when individual groups were analyzed, the difference from placebo was not significant for the 300 mg/day group.

2. By the end of the 6-month double-blind phase of Crofford et al, _____% of LYRICA patients remained on the study drug and maintained a therapeutic response compared to _____% of placebo patients.
   - A 61; 32
   - ***B*** ***53; 33***
   - C 51; 21
   - D 44; 13

Module Summary

(1) The efficacy and safety of LYRICA as monotherapy for the management of fibromyalgia were established across a clinical trial program that included 2 randomized, multicenter, controlled trials.

- **Arnold et al (Study F1):** 14-week, phase III, randomized, double-blind, placebo-controlled, fixed-dose trial in 745 patients, including a 2-week dose-escalation phase, and a 12-week maintenance phase randomized to LYRICA 300, 450, or 600 mg/day* or placebo; the study began with a 1-week placebo run-in phase to exclude placebo responders
- **Crofford et al (Study F2):** randomized withdrawal study starting with an open-label phase to exclude LYRICA nonresponders and followed by a 6-month phase to assess the durability of the effect of LYRICA in responders:
  - 6-week, open-label, dose optimization phase in which 1051 patients were treated with LYRICA 300, 450, or 600 mg/day* based on response and tolerability
  - responders (n = 566) were randomized to LYRICA or placebo for 26-week double-blind treatment; patients randomized to LYRICA received the dose that was optimized during the open-label phase (300 to 600 mg/day*)

Efficacy measures for Arnold et al (Study F1): The primary efficacy measure in the intent-to-treat (ITT) population was the endpoint mean pain score, which was derived from a daily pain diary recorded by patients using the Pain Intensity Numeric Rating Scale (PI-NRS). Co-primary efficacy measures included the Patient Global Impression of Change (PGIC), in which patients measure the change in their overall status from the beginning to the study endpoint, and the Fibromyalgia Impact Questionnaire (FIQ) total score.

Secondary efficacy measures included:

- Sleep Quality Score from the Daily Sleep Diary
- Medical Outcomes Study-Sleep (MOS-Sleep) Scale
- Multidimensional Assessment of Fatigue (MAF)
- Short-Form-36 Health Questionnaire (SF-36)
- Hospital Anxiety and Depression Scale (HADS)

Efficacy measures for Crofford et al (Study F2): The primary efficacy measure in the ITT population was the loss of therapeutic response, which was defined as reduction of <30% in pain scores from the open-label baseline of the study in 2 consecutive visits during the double-blind portion of the study or worsening of fibromyalgia symptoms that required the use of alternate treatment.

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* *LYRICA 600 mg/day is not an approved dose for fibromyalgia, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day in fibromyalgia, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended in fibromyalgia.*

The secondary efficacy measures included PGIC, FIQ, MOS-Sleep Scale, MAF, and SF-36, which were used to evaluate changes in pain-related sleep interference, fatigue, mood, and other patient-reported outcomes during treatment.

Secondary efficacy measures in both pivotal studies: The secondary endpoints are not included in the LYRICA prescribing information (except for FIQ and PGIC in Crofford et al); therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Patient selection criteria: Eligible patients were males or nonpregnant, nonlactating females of any race who were ≥18 years of age. To be randomized for treatment, patients had to meet the ACR criteria for a diagnosis of fibromyalgia and:

- have recorded a score of ≥40 mm on the Pain VAS at screening and enrollment/randomization
- be willing to comply with study procedures
- provide informed consent

Patients were excluded if they had evidence of inflammatory muscle or rheumatologic disease; were previous participants in a LYRICA clinical trial; had severe psychiatric illness (including major depressive disorder) or a severe medical illness; had creatinine clearance (CL_{cr}) ≤60 mL/min; had pending Worker's Compensation, Workman's Compensation, civil litigation, disability claims, or out-of-court settlements for claims pertinent to the subject's fibromyalgia; or were currently receiving monetary compensation as a result of any of these.

Data analysis and presentation: All clinical studies listed in the LYRICA product labeling were analyzed on an ITT basis using the baseline observation carried forward (BOCF) or modified baseline observation carried forward (mBOCF).

Intent-to-treat means the entire population of study subjects who were randomized and took at least 1 dose of study medication was included in the analysis of the study. In a BOCF analysis, if patients drop out of the trial, instead of using their last measurement while on treatment and carrying it forward (LOCF), their original baseline measurement is carried forward — eliminating any measurements they reported during the time they did receive treatment. The mBOCF analysis censors patients who discontinue due to adverse events so that their baseline score is carried forward, but carries the last observation forward for patients who discontinue for other reasons (eg, lost to follow-up).

Arnold et al (Study F1): The objective for Arnold et al was to evaluate the efficacy and safety of LYRICA compared with placebo treatment for the symptomatic relief of fibromyalgia.

In Arnold et al, 745 patients were randomized to:

- placebo
- LYRICA 300 mg/day (150 mg BID)
- LYRICA 450 mg/day (225 mg BID)
- LYRICA 600 mg/day (300 mg BID)*

In terms of the primary endpoints, compared with placebo, patients in all 3 LYRICA treatment groups had:

- significantly improved endpoint mean pain scores (based on BOCF analysis)
- significantly improved weekly mean pain scores beginning at week 1 and maintained to the study endpoint (except LYRICA 300 mg/day at week 11)
- a significantly greater proportion of ≥30% and ≥50% responders (LOCF)

In terms of the co-primary endpoints, compared with placebo, patients in all 3 LYRICA treatment groups had:

- significant improvements in PGIC
- significant improvement on the FIQ

Crofford et al (Study F2): In Crofford et al, the primary endpoint was the time to loss of therapeutic response (time to worsening). This was defined as either of the following:

- the time it took for a patient's responses on the Pain Visual Analogue Scale (Pain VAS) to worsen to within 30% of their open-label baseline score during 2 consecutive visits during the double-blind phase
- worsening of fibromyalgia symptoms necessitating an alternative treatment per the clinical judgment of the primary investigator

In Crofford et al, 1051 patients entered a 6-week, open-label, dose optimization phase; 566 of these patients entered the 26-week, double-blind, treatment phase and were randomized to placebo or LYRICA. Patients randomized to LYRICA remained at the optimized dose established during the open-label phase:

- LYRICA 300 mg/day (150 mg BID)
- LYRICA 450 mg/day (225 mg BID)
- LYRICA 600 mg/day (300 mg BID)*

In terms of the primary endpoint, time to loss of therapeutic response was significantly longer for subjects treated with LYRICA compared to those treated with placebo. PGIC and FIQ showed a significant benefit of LYRICA over placebo in terms of time to worsening.

** LYRICA 600 mg/day efficacy data are not to be detailed.*

Glossary

alpha$_2$-delta (α_2-δ)
an auxiliary subunit of voltage-gated calcium channels in central nervous system tissues that can be involved in the treatment of epilepsy and neuropathic pain

analgesic
a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness

BID
twice a day; abbreviation for the Latin *bis in die*

bioavailability
the physiologic availability of a given amount of a drug; proportion of the administered dose that is absorbed into the bloodstream

creatinine
a component of urine and the final product of creatine catabolism

creatinine clearance (CL_{cr})
measurement of the clearance of endogenous creatinine, used for evaluating the glomerular filtration rate (GFR)

diabetic peripheral neuropathy (DPN)
diabetes mellitus-related damage of the peripheral nervous system; can result in neuropathic pain

double-blind
a study in which neither the investigators nor the patients know what treatment the patients are receiving

intent-to-treat (ITT) population
the population of patients, including all those randomized to receive treatment, whether or not they completed the trial

glutamate
the major excitatory neurotransmitter of the CNS

fibromyalgia
a common condition characterized by the hallmark symptom of chronic, widespread pain; patients may also present with a wide range of symptoms, including tenderness, sleep disturbances, fatigue, and morning stiffness

mean
the average; usually assumed to be the arithmetic mean (sum of all values divided by number of values) unless otherwise specified

median
the middle value in a set of measurements

open-label
a study in which both investigators and patients know the identity of the medication

partial seizure
a seizure characterized by localized cerebral ictal onset; also called focal or localization-related seizure

pharmacokinetics
movements of drugs within biologic systems, as affected by uptake, distribution, binding, elimination, and biotransformation; particularly the rates of such movements

postherpetic neuralgia (PHN)
chronic severe, stabbing, or throbbing pain that continues after the visible evidence of an episode of shingles (herpes zoster) has resolved

serotonin
a chemical messenger (neurotransmitter) that has a variety of roles in regulating mood, behavior, and perception of pain

single-blind
a study in which one party, either the investigator or the participant, is unaware of what medication the participant is taking

somnolence
an inclination to sleep

substance P
a protein involved in nervous system function; stimulates smooth muscle contraction and the dilation of blood vessels; active in inflammation and pain transmission

voltage-gated calcium channel
a calcium ion channel that opens and closes in response to change in the electrical potential across the plasma membrane of the cell

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